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ORIGINAL ARTICLE

Pharmacokinetics and safety of olmesartan medoxomil in combination with either amlodipine or atenolol compared to respective monotherapies in healthy subjects

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ABSTRACT

The aim of this study was to investigate any influence on olmesartan plasma pharmacokinetics from amlodipine or atenolol. We analysed pharmacokinetics and safety of olmesartan medoxomil in combination with either amlodipine or atenolol compared to respective monotherapies in two separate studies. In one study, 18 subjects received once daily treatment for 7 days with olmesartan medoxomil 20 mg alone or with amlodipine 5 mg or amlodipine 5 mg alone. In the other study, atenolol 50 mg once daily replaced amlodipine. Concentration vs. time profiles for olmesartan monotherapy were similar to combination therapy. Mean olmesartan $AUC_{ss,\tau}$ for olmesartan alone and with amlodipine were 2439 and 2388 ng h/mL and for olmesartan alone and with atenolol were 2340 and 2247 ng h/mL. Corresponding olmesartan $C_{ss,max}$ values were 465.7 and 439.5 ng/mL for amlodipine, and 447.4 and 423.8 ng/mL for atenolol. Median t_{max} values for olmesartan were 1.5 h for each group in each study. Bioequivalence was established for all pharmacokinetic parameters. Lack of significant pharmacokinetic interactions between olmesartan and amlodipine or atenolol provides a basis for combination therapy.

INTRODUCTION

Hypertension is the leading causal factor contributing to cardiovascular disease worldwide, with an estimated 49% of all ischaemic heart disease and 62% of all cerebrovascular disease cases attributable to hypertension [1]. Depending on cardiovascular risk, guidelines for management of hypertension recommended by international advisory bodies in both Europe and North America suggest targets for systolic blood pressure (SBP) and diastolic blood pressure (DBP) of lower than 140 or 130 mmHg and 90 or 80 mmHg, respectively [2–4]. These guidelines also acknowledge that many patients will require combinations of two or more antihypertensive drugs to achieve these targets [2–4]. As a consequence, treatment for hypertension involves a significant and increasing use of combination regimens, and the development of new combination algorithms by combining established agents with newer compounds. The importance of combinations of antihypertensive agents as first-line therapy is increasing and this is reflected in the most recent treatment guidelines [2–4]. The greater role for combination therapy in the treatment of hypertension generates an increasing need for pharmacokinetic studies to investigate potential interactions between agents that will be used in combination therapy. Among the combinations of anithypertensives currently recommended in guidelines [4], those based on

angiotensin II receptor blockers (ARBs) and calcium channel blockers (CCBs) are of special interest. In this regard, olmesartan medoxomil represents a highly selective and potent ARB inhibiting angiotensin binding to subtype 1 receptors (AT_1) [5,6]. In clinical trials involving more than 3500 patients with hypertension, olmesartan medoxomil has been shown to produce clinically significant decreases in blood pressure, with a tolerability profile similar to placebo [7]. In comparison to other ARBs olmesartan was also shown to be very effective at reducing DBP [8]. Furthermore, olmesartan medoxomil reduced both DBP and SBP more effectively than the angiotensin-converting enzyme inhibitor captopril and reduced SBP more effectively than the β-blocker atenolol [9]. The CCB amlodipine is also a very effective antihypertensive agent [10] with a rapid onset of action that was linked to improved outcomes in terms of myocardial infarction and stroke relative to the ARB valsartan [11]. Amlodipine has been shown to have similar antihypertensive efficacy to olmesartan [12]. In a direct comparison, olmesartan and amlodipine were shown to have a similarly rapid onset of efficacy, although a greater proportion of patients achieved target BP goals with olmesartan compared with amlodipine [12,13]. As an alternative to CCBs, many patients with compelling indications such as cardiac diseases including heart failure or dysrhythmias are also treated with a β-blocker in addition to an ARB [4]. Agents such as β-blockers and CCBs are therefore widely available antihypertensive treatments that are commonly combined with agents from other classes to improve efficacy. The availability of potent new agents such as olmesartan offers the possibility to generate combined treatment regimens with the potential of greater antihypertensive efficacy. Thus, the combination between olmesartan and these agents requires that the potential of pharmacokinetic interactions between olmesartan and either agent should be investigated. Consequently, two separate phase I trials with identical designs were conducted to evaluate potential pharmacokinetic interactions in healthy, adult subjects when olmesartan medoxomil is used in combination with either the CCB amlodipine or the β-blocker atenolol. The safety and tolerability of these combinations were also assessed.

MATERIALS AND METHODS

Study design

These two single-centre trials used an identical randomized, open-label, three-way crossover design that comprised three treatment periods, each of 7 days duration with a 7–14 day washout between the first and second; and second and third treatment period. In one trial, subjects received 7 days of treatment with: olmesartan medoxomil alone; olmesartan medoxomil plus amlodipine; or amlodipine alone. In the other trial, the design was similar but subjects received atenolol instead of amlodipine.

Each trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP). All subjects in each trial provided written informed consent before entering the trial.

The primary objectives of these trials were to investigate any possible influence of amlodipine or atenolol on the steady-state pharmacokinetics of olmesartan, the pharmacologically active metabolite of olmesartan medoxomil, and to study any possible influence of olmesartan medoxomil on the steady-state pharmacokinetics of amlodipine or atenolol. Secondary objectives included evaluation of the renal elimination (through analysis of pharmacokinetic parameters in urine) of olmesartan and amlodipine or atenolol after multiple dosing and assessment of the safety and tolerability of these treatments.

Subjects

In each of the two trials, 18 healthy, adult males aged 18–45 years were included if they had normal blood pressure (SBP ≤140 and DBP ≤90 mmHg) and displayed no clinically relevant abnormality in physical examination, electrocardiogram (ECG) or laboratory findings that might interfere with trial objectives and were negative for human immunodeficiency virus antibody, hepatitis B surface antigen and hepatitis C virus tests.

The main exclusion criteria included: use of any medication in the 7 days before the start of the trial; a history or clinical evidence of significant cerebrovascular, gastrointestinal, haematological or hepatic disease, myocardial infarction; previous history of any serious disease (including immunocompromised and/or neutropenic subjects); clinical evidence of renal disease; clinically significant laboratory abnormalities; a body mass index <19 or >28 kg/m^2 or weight <45 kg or >95 kg.

Interventions

After screening, subjects began active treatment no more than 4 weeks later. On day 1, subjects began the first of the three treatment periods by being randomly allocated to one of six possible treatment sequences (ABC, ACB, BAC, BCA, CAB or CBA) using a randomization list generated

by Sankyo Pharma GmbH (now Daiichi Sankyo Europe GmbH, Munich, Germany) using SAS version 6.12 software. The treatment sequence determined the order in which subjects received treatments. In one trial, subjects were treated with: A – olmesartan medoxomil 20 mg once daily (Sankyo Pharma, Pfaffenofen, Germany [now Daiichi Sankyo Europe GmbH]); B – olmesartan medoxomil 20 mg once daily plus amlodipine 5 mg once daily (Pfizer GmbH, Karlsruhe, Germany); and C – amlodipine 5 mg once daily. In the other trial, amlodipine was replaced by atenolol 50 mg once daily (Ratiopharm GmbH, Ulm, Germany). Subjects then received the other two treatments according to the defined sequence. Each treatment period lasted 7 days and after the last dose of study medication in the first and second treatment periods there was a treatment-free washout (7–14 days for the atenolol study, and 14 days for the amlodipine study) before subjects entered the next treatment period.

Each trial was conducted in a single centre in Görlitz, Germany. In each trial, all subjects were admitted to the trial centre approximately 12 h before dosing on day 1 of each treatment period and remained at the site until all assessments had been carried out on day 8. Subjects were permitted to leave the trial centre during the washouts. After the end of the third treatment period, subjects remained at the centre until a final examination had been carried out on day 9.

ASSESSMENTS

Pharmacokinetics

During all treatment periods in each trial, all doses of medication were taken orally with 200 mL water at 08:00 (±1 h) after an overnight fast. On days 1–6, subjects received a standardized breakfast immediately after intake of study medication, a standardized lunch approximately 4 h after dosing and another standardized meal 8–10 h after dosing. On day 7, subjects were given breakfast after the 4-h blood sample was taken, lunch approximately 7 h after dosing and the last meal approximately 11 h after dosing. In each treatment period in both trials, blood samples (6 mL) for pharmacokinetic analysis were taken on day 7 immediately before dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 20 and 24 h after dosing. Further blood samples for pharmacokinetic analysis were taken on day 8.

Subjects were not permitted to use any other medication, including over the counter preparations from 7 days before the first day of the first treatment period until the end of the trial.

Blood samples were collected in lithium-heparin tubes and separated by centrifugation into plasma, which was frozen at –20 °C and stored until analysis. Plasma concentrations of olmesartan (RNH-6270), the active metabolite of olmesartan medoxomil, were determined using a validated high performance liquid chromatography system with a lower limit of quantification of 0.41 ng/mL. Amlodipine concentrations were determined using a validated reverse phase liquid chromatography/tandem mass spectrometry system, with a lower limit of quantification of 0.1 ng/mL. Concentrations of atenolol were determined using a liquid chromatography/tandem mass spectrometry method, validated according to good laboratory practice with a lower limit of quantification of 1.01 ng/mL. Concentrations of olmesartan and amlodipine were measured by Simbec Research Ltd (Mid Glamorgan, South Wales, UK) and atenolol by A&M Labor für Metabolismusforschung, Service GmbH (Bergheim, Germany).

Other assessments

At the screening visit, demographic and anthropometric data were recorded and subjects provided medical and surgical histories. Checks on the use of concomitant medication were made at screening and on days 1–8 of each treatment period and checks on the dispensing of medication and compliance were made on days 1–7.

Safety and tolerability

Subjects underwent physical examinations at screening and at the final examination or premature termination. Trough blood pressure and pulse rates were measured at screening and on days 1–8 and at the final examination or premature termination. In addition, peak blood pressure and pulse rates were measured 4 ± 1 h after administration of medication on days 1 and 7. Routine laboratory tests were made at screening, and on days 1 and 7 and at the final examination. Twelve-lead electrocardiogram recordings were also made on these days, except for day 7.

Information on adverse events was collected on days 1–8, and at the final examination or premature termination visit, and where required, for up to 14 days after each study.

Statistical analysis

Pharmacokinetic parameters were calculated from plasma concentrations measured in the samples taken on days 7 and 8 of each treatment period for olmesartan, amlodipine and atenolol using a non-compartmental

model. The pharmacokinetic parameters that were evaluated for olmesartan, amlodipine and atenolol were the maximum steady-state concentration ($C_{ss,\ max}$), the time to reach $C_{ss,max}$ (t_{max}), the concentration area under the curve at steady-state during one dosing interval 0 to τ = 24 h after the last dose on day 7 of each treatment period ($AUC_{SS,\tau}$) and the apparent steady-state volume of distribution (V_{SS}/f).

The parameter $AUC_{SS,\tau}$ was calculated using the linear trapezoidal rule with V_{SS}/f derived from $V_{SS}/f = CL_{SS}/f \times MRT_{SS}$ where CL_{SS}/f is the steady-state oral clearance calculated as CL_{SS}/f = dose/$AUC_{SS,\tau}$ and f is the unknown fraction of dose absorbed. The steady-state mean residence time (MRT_{SS}) is extrapolated to infinity using the equation: $MRT_{SS} = [AUMC_{SS,\tau} + \tau(AUC_{SS,0-\infty} - AUC_{SS,\tau})]/AUC_{SS,\tau}$ where $AUMC_{SS,\tau}$ is the area under the time curve from dosing until τ and $AUC_{SS,0-\infty}$ is the steady-state AUC extrapolated to infinity using $AUC_{SS,0-\infty} = AUC_{SS,0-tz} + C_z/\lambda_z$ in which $AUC_{SS,0-tz}$ is the area under the concentration–time curve at steady-state up to the last time point t_z for which there is a measurable serum concentration ($C_z \geq$ limit of quantification) and λ_z is the terminal rate constant derived by log-linear regression on the terminal elimination phase of the plasma concentration–time profiles.

Statistical analysis was carried out by calculating arithmetic means and standard deviations, geometric means, medians and maximum and minimum values for continuous data and absolute and relative frequencies for categorical data.

Treatments were compared on a test vs. reference basis as follows: olmesartan plus amlodipine or atenolol vs. olmesartan and olmesartan plus amlodipine or atenolol vs. amlodipine or atenolol. Treatment comparisons involved two one-sided equivalence hypothesis testing with a significance of $\alpha = 0.05$. Equivalence of $AUC_{ss,\tau}$ and $C_{ss,max}$, was investigated using an ANOVA model appropriate for the crossover design using log-transformed values. For t_{max}, a non-parametric approach was used on untransformed data.

Bioequivalence was assessed by comparing relative bioavailability ($AUC_{ss,\tau}$), peak plasma concentration ($C_{SS,max}$) and the time to reach peak plasma concentration (t_{max}) for combination therapy vs. monotherapy. Bioequivalence was established if the geometric mean ratios of $AUC_{ss,\tau}$ and $C_{SS,max}$ were shown to be equivalent [i.e. lay within the range 80–125% with 90% confidence interval (CI)]. For t_{max}, equivalence was established if the 90% CI was included in the range defined by ±20% of the median t_{max} value for monotherapy [14].

Pharmacokinetic analyses were evaluated in all subjects for whom analysis of blood and urine samples were carried out (pharmacokinetic set). Analysis of safety and tolerability data was carried out in all subjects randomized to treatment who had received at least one dose of study medication (safety set).

Summary statistics was tabulated to assess safety and tolerability for adverse events, laboratory tests, electrocardiogram results, blood pressure and pulse rate.

RESULTS

Study populations

Of the 51 subjects screened in the amlodipine trial, 18 were randomized to treatment. In the atenolol trial, 50 subjects were screened and 18 were randomized to treatment. There were no dropouts or withdrawals in either trial and the number of subjects who completed each trial (i.e. the safety set) was 18. There were no major protocol violations in either study and the number of subjects in the pharmacokinetic set in each study was also 18. The demographic and baseline characteristics of both safety sets are given in *Table I*.

Table I Demographic and baseline characteristics of subjects evaluated in the amlodipine and atenolol pharmacokinetic analyses (Safety sets, n = 18 for each trial).

	Olmesartan plus amlodipine[a]	Olmesartan plus atenolol[b]
Age (years)	27.9 ± 7.9 (27.5, 19.0–44.0)	28.9 ± 8.0 (25.5, 20.0–44.0)
Weight (kg)	68.9 ± 8.7 (68.0, 58.0–94.0)	71.3 ± 10.5 (73.0, 55.0–90.0)
Height (cm)	177 ± 5.7 (176, 163–191)	176.2 ± 7.1 (177.0, 162.0–190.0)
Body mass index (kg/m^2)	22.1 ± 2.1 (21.8, 19.2–26.0)	22.9 ± 2.5 (22.4, 19.0–26.6)
Alcohol consumption		
None	7 (38.9)	0
Sporadic	11 (61.1)	18 (100)
Smoking status		
Yes	12 (66.7)	14 (77.8)
No	3 (16.7)	3 (16.7)
Ex-smoker	3 (16.7)	1 (5.6)

Continuous data are means ± standard deviations (median, range). Categorical data are numbers with percentages.

[a]Subjects entered into the olmesartan plus amlodipine combination group acted as their own controls, i.e. after the respective monotherapy treatment with either olmesartan or amlodipine.

[b]Subjects entered into the olmesartan plus atenolol group acted as their own controls, i.e. after the respective monotherapy treatment with either olmesartan or atenolol.

PHARMACOKINETICS

Olmesartan and amlodipine

The concentration vs. time profile for olmesartan during olmesartan medoxomil monotherapy was similar to that observed during combination therapy (*Figure 1a*). Similarly, the concentration vs. time profile for amlodipine during amlodipine monotherapy was similar to that seen during combination therapy (*Figure 1b*).

The mean $AUC_{ss,\tau}$ and $C_{ss,max}$ values for olmesartan were similar during monotherapy and combination therapy (*Table II*). The 90% CIs for the ratios of the geometric means fell within the acceptance ranges, demonstrating bioequivalence for each parameter. The median t_{max} values were identical and bioequivalence was also established for this parameter.

For the comparison of amlodipine monotherapy with combination therapy, bioequivalence was also established for $AUC_{ss,\tau}$, $C_{ss,max}$ and t_{max}.

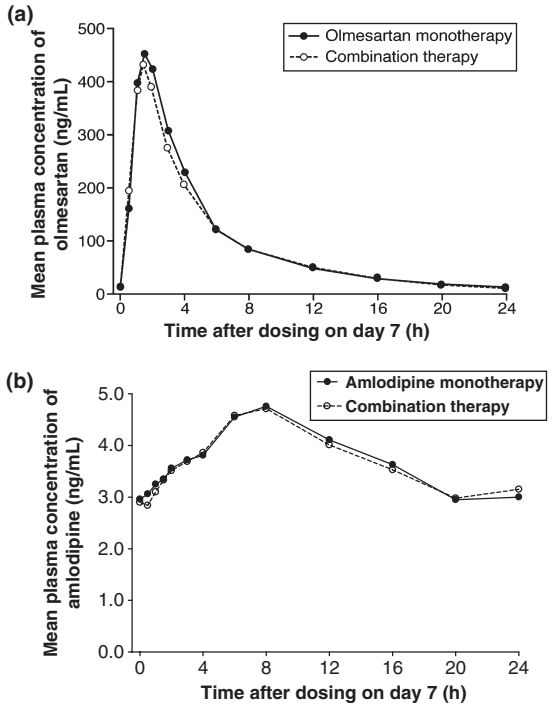

Figure 1 (a) Mean plasma concentration vs. time curve for olmesartan during administration of olmesartan medoxomil monotherapy and combination therapy with olmesartan medoxomil plus amlodipine. (b) Mean plasma concentration vs. time curve for amlodipine during administration of amlodipine monotherapy and combination therapy with olmesartan medoxomil plus amlodipine.

Co-administration of olmesartan and amlodipine had a negligible effect on mean renal clearance at steady-state for each agent relative to that obtained with separate administration. For olmesartan, the mean urinary clearance rate was 13.4 mL/min during monotherapy compared with 12.5 mL/min during combination therapy. For amlodipine, the mean urinary clearance rate was 43.7 mL/min during monotherapy compared with 47.7 mL/min during combination therapy.

Olmesartan and atenolol

The concentration vs. time profile for olmesartan was similar during olmesartan medoxomil monotherapy and combination treatment with olmesartan medoxomil plus atenolol (*Figure 2a*). Similarly, the concentration vs. time profile for atenolol was similar during atenolol monotherapy and treatment with olmesartan medoxomil plus atenolol (*Figure 2b*).

The mean $AUC_{ss,\tau}$ and $C_{ss,max}$ values for olmesartan were similar for monotherapy and combination therapy (*Table III*). The 90% CIs fell within the acceptance ranges confirming bioequivalence for each parameter. Median t_{max} values were also identical, demonstrating bioequivalence for this parameter.

For the comparison of atenolol monotherapy with combination therapy, bioequivalence was demonstrated for $AUC_{ss,\tau}$ and $C_{ss,max}$, but not t_{max}.

Co-administration of olmesartan and atenolol had a negligible effect on mean renal clearance at steady-state for each agent relative following separate administration. For olmesartan, the mean urinary clearance rate was 12.6 mL/min during monotherapy compared with 12.9 mL/min during combination therapy. For atenolol, the mean urinary clearance rate was 116.3 mL/min during monotherapy compared with 112.5 mL/min during combination therapy.

Safety and tolerability

Throughout each trial there were no serious adverse events, all adverse events were of mild or moderate intensity and no subjects withdrew due to adverse events. Only one adverse event (headache) occurred in the amlodipine trial (*Table IV*). In the atenolol trial, a total of eight adverse events were reported by six subjects. The most frequent of these was mild bradycardia (heart rate <50 beats/min), with four cases in three subjects (*Table IV*). The other adverse events were hypertriglyceridaemia, influenza-like illness, leucocytosis and an increase in alanine aminotransferase.

Table II Mean values for primary pharmacokinetic parameters for olmesartan and amlodipine given as monotherapy and as combination therapy with the results of bioequivalence testing (pharmacokinetic set $n = 18$).

Parameter ($n = 18$)	Substance	Treatment ($n = 18$)		Point estimate (combination/ monotherapy)[a]	90% CI	Acceptance range	Equivalence
		Monotherapy	Combination therapy				
$AUC_{SS,\tau}$ (ng h/mL)[b]	Olmesartan	2439 (17.1)	2388 (16.9)	0.98	0.93, 1.03	0.80, 1.25	Yes
	Amlodipine	87.8 (22.6)	86.5 (26.3)	0.99	0.95, 1.02	0.80, 1.25	Yes
$C_{SS,max}$ (ng/mL)[b]	Olmesartan	465.7 (22.2)	439.5 (26.7)	0.94	0.89, 1.00	0.80, 1.25	Yes
	Amlodipine	4.76 (22.2)	4.69 (27.2)	0.99	0.95, 1.03	0.80, 1.25	Yes
t_{max} (h)[c]	Olmesartan	1.50 (1.50, 3.00)	1.50 (1.00, 2.00)	−0.25	−0.25, 0.00	−0.35, 0.35	Yes
	Amlodipine	8.00 (6.00, 12.00)	8.00 (6.00, 8.00)	0.00	0.00, 0.00	−1.49, 1.49	Yes

[a]Ratio of the geometric means for $AUC_{SS,\tau}$ and $C_{SS,max}$; median of all possible pair-wise differences between treatment regimens for t_{max}.
[b]Geometric mean (geometric coefficient of variation, given as a percentage).
[c]Median (min, max).

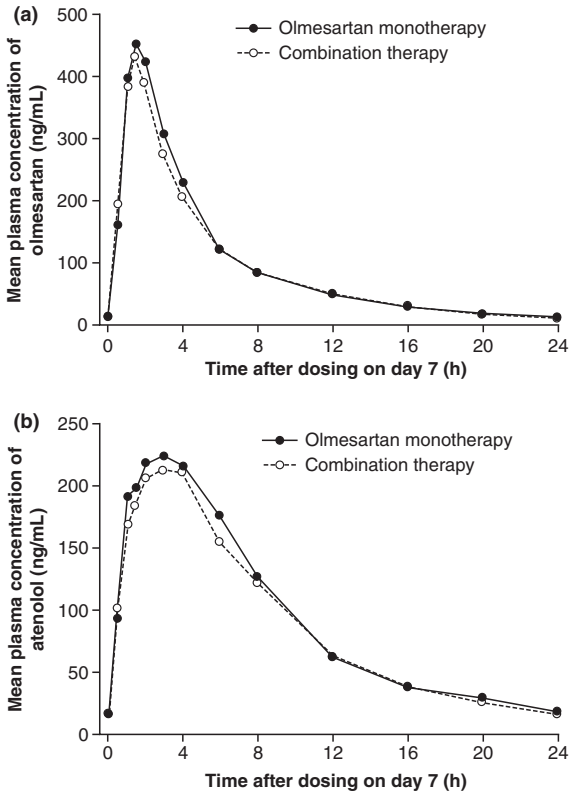

Figure 2 (a) Mean plasma concentration vs. time curve for olmesartan during administration of olmesartan medoxomil monotherapy and combination therapy with olmesartan medoxomil plus atenolol. (b) Mean plasma concentration vs. time curve for atenolol during administration of atenolol monotherapy and combination therapy with olmesartan medoxomil plus atenolol.

DISCUSSION

The results of these two studies show that exposure to olmesartan, the pharmacologically active component of olmesartan medoxomil is unaffected by co-administration with either amlodipine or atenolol. Furthermore, exposure to both amlodipine and atenolol is unaffected by co-administration with olmesartan medoxomil. The pharmacokinetic profile obtained for olmesartan in this trial is similar to previously reported data (steady-state $AUC_{0-24\ h}$, = 2009 ng h/mL, C_{max} = 376 ng/mL, t_{max} = 1.5 h) [15]. This validates the approach and methods used here and highlights the excellent reproducibility of olmesartan pharmacokinetics. Moreover, all treatments were well tolerated and there was a low level of adverse events with no withdrawals or serious adverse events, which agrees with the excellent tolerability profile previously reported for olmesartan [7].

It has been proposed that the favourable pharmacokinetic profile of olmesartan limits its potential for clinically significant drug interactions [15,16]. This expectation was indeed confirmed in the current investigations, in which plasma pharmacokinetics of olmesartan were similar for olmesartan medoxomil given as monotherapy or in combination with either amlodipine or atenolol. Specifically, the rate and extent of absorption of olmesartan at steady-state were unaffected by co-administration with atenolol or amlodipine, as shown by the demonstration of bioequivalence for $AUC_{ss,\tau}$, $C_{ss,max}$ and t_{max} when comparing monotherapy with combination therapy. Furthermore, in each study the mean $AUC_{ss,\tau}$ and $C_{ss,max}$ values for olmesartan monotherapy differed by less than 10% from the respective combination therapy values. Likewise, the steady-state plasma pharmacokinetics of amlodipine and atenolol was similar for each agent given as monotherapy and in combination with olmesartan. Bioequivalence for amlodipine and atenolol administered alone or in combination with olmesartan medoxomil was demonstrated for $AUC_{ss,\tau}$,

Table III Mean values for primary pharmacokinetic parameters for olmesartan and atenolol given as monotherapy and as combination therapy with the results of bioequivalence testing (**p**harmacokinetic set $n = 18$).

Parameter	Substance	Treatment		Point estimate (combination/ monotherapy)[a]	90% CI	Acceptance range	Equivalence
		Monotherapy	Combination therapy				
$AUC_{SS,\tau}$ (ng h/mL)[b]	Olmesartan	2340.5 (22.0)	2247.8 (21.4)	0.96	0.88, 1.05	0.80, 1.25	YES
	Atenolol	2181.8 (21.6)	2048.5 (27.7)	0.94	0.84, 1.05	0.80, 1.25	YES
$C_{SS,max}$ (ng/mL)[b]	Olmesartan	447.4 (23.2)	423.8 (20.0)	0.95	0.86, 1.05	0.80, 1.25	YES
	Atenolol	250.0 (24.1)	238.0 (26.2)	0.95	0.84, 1.08	0.80, 1.25	YES
t_{max} (h)[c]	Olmesartan	1.50 (1.00, 3.00)	1.50 (1.00, 2.00)	0.00	−0.25, 0.00	−0.33, 0.33	YES
	Atenolol	3.00 (1.00, 6.00)	3.00 (1.00, 4.00)	−0.25	−0.75, 0.00	−0.59, 0.59	NO

[a]Ratio of the geometric means for $AUC_{SS,\tau}$ and $C_{SS,max}$; median of all possible pair-wise differences between treatment regimens for t_{max}.
[b]Geometric mean (geometric coefficient of variation, given as a percentage).
[c]Median (min, max).

Table IV Frequency of treatment-emergent adverse events and relationship to treatment in each trial (**s**afety sets).

	Number of reports	Classification of adverse event	Relationship to treatment
Olmesartan–amlodipine trial ($n = 18$)			
Olmesartan	0		
Amlodipine	0		
Olmesartan plus amlodipine	1	Headache	Possible
Total	1		
Olmesartan–atenolol trial ($n = 18$)			
Olmesartan	1	Hypertriglyceridaemia	Unlikely
	1	Influenza-like illness	Unrelated
Atenolol	2	Bradycardia	Possible
	1	Leucocytosis	Unrelated
Olmesartan plus atenolol	2	Bradycardia	Possible
	1	Increased alanine aminotransferase	Possible
Total	8		

and $C_{ss,max}$ but not for t_{max}, where bioequivalence could only be demonstrated for amlodipine. The latter finding was probably due to the larger variation of values observed in the atenolol monotherapy group and despite the fact that median t_{max} values for atenolol were identical after mono- and combination therapy. It appears possible that equivalence could have been achieved if a larger group of individuals would have been studied. Overall and in agreement with previous studies analysing other antihypertensive compounds as comparator to amlodipine or atenolol [17,18], our study clearly shows that there are also no relevant pharmacokinetic interactions between olmesartan and either of these agents. Although the nature of the investigations performed in these studies made enrolment of large patient numbers practically difficult, it should be noted that these studies used a crossover design. This effectively minimizes variation caused by confounding variables such as smoking, age and alcohol consumption since each patient acts as his own control throughout the study period.

There are practical implications of these results for hypertension management. Firstly, it is acknowledged by current hypertension management guidelines in North America and Europe that combination therapy is required to achieve goal BP in many patients, since this leads to greater overall BP reductions compared with monotherapy, owing to additive and/or synergistic effects between different classes of antihypertensive drugs [2,4,19]. This reality is reflected in the design of recent clinical trials, many of which have used combinations of at least two antihypertensive agents to allow patients to achieve target blood pressures [4,20]. Among such trials are those that have combined olmesartan medoxomil with other antihypertensive agents, such as hydrochlorothiazide and amlodipine [21,22]. The results of these studies confirm that the combination of olmesartan with antihypertensive agents from other classes leads to greater reductions in BP than achieved by monotherapy with either agent alone. In this context, it is important that significant pharmacokinetic interactions between olmesartan and other antihypertensive agents (such as amlodipine or atenolol) that could lead to adverse effects are excluded. The results of the present studies provide some reassurance that adverse interactions at a pharmacokinetic level between olmesartan and either amlodipine or atenolol are unlikely. This finding

fits with the general principles of combination antihypertensive therapy, which holds that pharmacokinetic interactions are generally of less significance than pharmacodynamic issues. The latter explains why the choice of components for an antihypertensive combination is generally made to provide differing yet complementary mechanisms rather than similar or identical actions.

In conclusion, the results of the current study demonstrate that the active metabolite of olmesartan medoxomil shows no pharmacokinetic interaction with amlodipine or atenolol and suggest that there should be no clinically relevant pharmacokinetic interactions between olmesartan and these agents.

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